Asian Journal of Chemistry; *Vol. 23, No. 11 (2011), 5169-5170*

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

One-Pot Preparation of 3-Hydroxymethyl 2,5-Diketopiperazine for Total Synthesis of Peticinnamin E

DEQUN SUN*, LI SUN, MIN LUO and ZHAOPIN GOU

Marine College, Shandong University, Weihai 264209, P.R. China

*Corresponding author: E-mail: dequn.sun@sdu.edu.cn

(*Received*: 14 January 2011; *Accepted*: 30 July 2011) AJC-10240

3-Hydroxymethyl 2, 5-diketopiperazine is a structure unit of pepticinnamin E, a natural product and a bi-substrate inhibitor of FPTase. In this paper, a facile synthetic strategy was developed to prepare 3-hydroxymethyl 2, 5-diketopiperazine with high yield.

Key Words: 2,5-Diketopiperazines analogue, Catalytical hydrogenation, Cyclization, Pepticinnamin E.

The pepticinnamin E was isolated[1] from Sereptomyces. OH-4652, which was identified as the potent FPTase inhibitor and was first synthesized by Prof. Waldmann's group[2]. Their research showed that pepticinnamin E is a bisubstrate inhibitor and until now, pepticinnamin E has been the only bisubstrate inhibitor produced from nature. There are five components in the structure of pepticinnamin E: the pentenyl phenyl acrylic acid[3], the new DOPA analogue[4], N-methylated-L-phenylalanine, D-tyrosine and 3-hydroxymethyl 2,5-diketopiperazine. Developing new methods to synthesize these components is necessary in order to complete the synthesis of pepticinnamin E and its analogues. These new methods are also important for the study of the structure-activity relationship between pepticinnamin E derivatives and the inhibition to FPTase. Diketopiperazine derivatives is not only a component in bioactive nature products[1,5], but also is an important pharmacophore group and very useful in study of molecular recognition[6]. In this work, we report a facile and large-scale preparation of 3-hydroxymethyl 2,5-diketopiperazine in one-pot reaction under mild condition.

General: Melting points were determined with an electrothermal digital melting point apparatus and were uncorrected. Optical rotations were recorded on a Perkin-Elmer Model 341 polarimeter, at the sodium D line. Elemental analyses were recorded on Carlo-1106 model automatic instrument. Infrared spectra (IR) were run on Nicolet MX-1 and Nicolet-560 MAGNA. ^{1}H NMR and spectra were run either on Bruker-200 and Bruker-300 or on Varian-400 at 25 ºC; ^{13}C NMR was given by Bruker-200 at 25 ºC. MS-EI mass spectra were obtained on V.G.7070E. All solvents were handled with standard ways before use.

Preparation of N-Cbz-D-Ser. 1: To a suspension of D-Ser. OH (1.051 g, 10 mmol) and powdered Na_2CO_3 (1.07 g) in 8 mL of water was added dropwise the CbzCl (1.76 mL, 12 mmol). The mixture was stirred at room temperature for 4 h and then acidified by 0.1N HCl solution to pH = 3-4. The reaction mixture was extracted with EtOAc three times (30 mL × 3) and the combined organic layer was washed by brine and concentrated in vacuo to give **1** (2.14 g, yield 89.9 %) as white solid. m.p. 189-190 ºC; $[\alpha]_D^{28}$ = -40.7 (c = 0.55, CH_2Cl_2); IR (KBr, ν_{max}, cm^{-1}): 3419, 3317, 3258, 3060, 1747, 1699, 1533, 1305, 1246, 1209, 1059, 1028, 749, 697, 610; ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.38 (s, 5H, ArH), 5.04 (s, 2H, OCH_2), 4.07 (m, 1H, α-CH), 3.65 (d, 2H, β-CH_2); MS-EI (m/z): 239 (M^+).

Preparation of N-Cbz-D-Ser.-GlyOMe dipeptide 3: To a solution of Cbz-D-SerOH **1** (0.602 g, 2.52 mmol) and N-methyl morpholine (NMM) (0.28 mL, 2.52 mmol) in freshly distilled THF (8 mL) was added dropwise ClCOOBu^i (0.35 mL, 2.77 mmol) at 0 ºC. After being stirred at the same temperature for 5 min, the solution of Gly·OMe·HCl **2** (0.348 g, 2.77 mmol) in N-methyl morpholine (0.31 mL, 2.77 mmol) and anhydrous DMF (5 mL) was added dropwise at 0 ºC. The mixture was kept stirring at the same temperature for 1 h, then warmed to room temperature and stirred for 0.5 h. Diluted with 100 mL of EtOAc and washed sequently by cold 5 % Na_2CO_3 solution, 1N HCl solution and brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give slight yellow syrup, which was purified by flash column chromatography on a silica gel to obtain **3** (0.662 g, yield 84.9 %) as white solid. m.p. 92-93 ºC; $[\alpha]_D^{28}$ = -25.7 (c = 0.50,

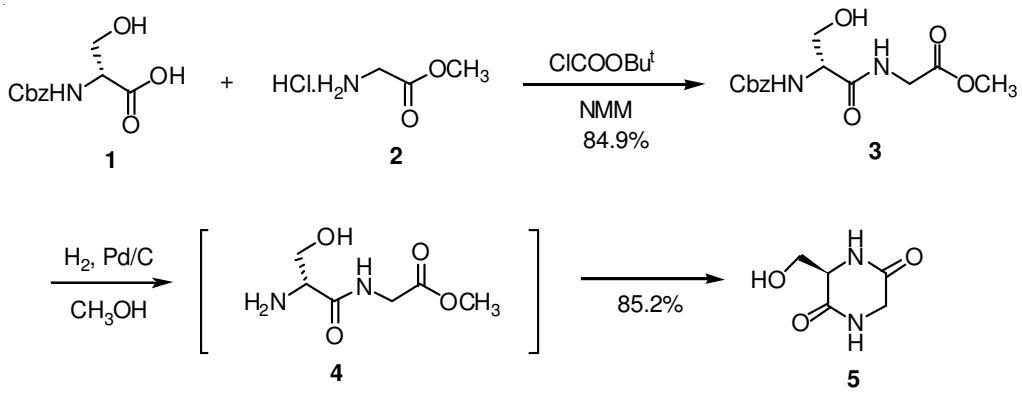

Fig. 1. Synthesis of 3-hydroxymethyl-2,5-diketopiperazine

CH_2Cl_2); Anal. calcd. (%) for $C_{14}H_{18}N_2O_6$: C 54.19, H 5.8, N 9.03; found (%): C 53.97, H 5.99, N 8.99. IR (KBr, ν_{max}, cm^{-1}): 3304, 2954, 1767, 1692, 1658, 1539, 1278, 1246, 1205, 1062, 1028, 698; ^1H NMR (400 MHz $CDCl_3$) δ ppm: 7.33 (s, 5H, ArH), 7.04 (bs, 1H, NH), 5.87 (d, J = 6.4 Hz, 1H, NH), 5.12 (s, 2H, OCH_2Ph), 4.29 (m, 1H, OH), 4.07-3.97 (m, 3H, α-CH, α-CH_2), 3.73 (s, 3H, OCH_3), 3.70 (m, 2H, β-CH_2O); MS-FAB (m/z): 311 (M^+ + 1).

Preparation of 3-hydroxymethyl 2,5-diketopiperazine 5: The suspension of dipeptide **3** (4 g, 12.9 mmol) and 10 % Pd/C (0.4 g, 10 % wt) in 30 mL of methanol was hydrogenated under H_2 at room temperature for *ca.* 6 h until no NH_2 group indicated by ninhydrin reaction or TLC showed the intermediate **4** was consumed completely. The solid in reaction was filtered off through a celite pad and the solid was washed by hot methanol. The combined filtrate was concentrated *in vacuo* to give colorless syrup, which was recrystallized to give **5** (1.58 g, yield 85.2 % for two steps) as white solid. m.p. 211-213 ºC; $[\alpha]_D^{28}$ = -39.7(c = 0.51, H_2O); Anal. calcd. (%) for $C_5H_8N_3O_3$: C 41.67, H 5.56, N 19.44; found (%): C 41.60, H 5.60, N 19.43. IR (KBr, ν_{max}, cm^{-1}): 3429, 3213, 2927, 1697, 1669, 1476, 1338, 1265, 1067, 832, 797, 588; ^1H NMR (300 MHz, D_2O) δ ppm: 4.13 (bs, 1H, Ser-CH), 4.14-4.08(d, J^2 = 18Hz, 1H, Gly-CH_2), 4.00-3.94 (d, J^2 = 18 Hz, 1H, Gly-CH_2), 4.03-3.98 (dd, J^2 = 12 Hz, J^3 = 2.7 Hz, 1H, Ser-OCH_2), 3.81-3.76 (dd, J^2 = 12 Hz, J^3 = 2.7 Hz, 1H, Ser-OCH_2); MS-FAB (m/z): 145(M^+ + 1).

Many methods for preparation of diketopiperazine derivatives, especially the 2,5-diketopiperazine derivatives were reported in literatures[7]. The most widely used strategy is solid phase synthesis with excellent yield, however, the workup procedure is normally cumbersome and also it is not easy to make scaleup preparation by this method in laboratory. We therefore, converted protected dipeptide **3** directly into target compound **5** in solution reaction, especially without isolation of dipeptide **4** since the free amine group in **4** generated *in situ* after hydrogenation could cyclize automatically without using coupling reagent, such as HOBt, EDCI. However, it is critical to determine if **4** was really consumed completely in reaction before reaction was ceased. Otherwise, it could be very difficult to obtain the pure product. Through such methodology, after simple workup procedure, the target **5** can be synthesized under very mild condition in large amount with good overall yield of 72.3 % (Fig. 1).

Conclusion

A facile synthetic method was exploited to prepare 3-hydroxymethyl 2,5-diketopiperazine in large scale with good overall yield *via in situ* cyclization after cleavage of Cbz group by catalytic hydrogenation.

REFERENCES

1. (a) S. Omura and H. Tomoda, *Pure Appl. Chem*., **66**, 2267 (1994); (b) S. Omura, V.D. der Pyl, J. Inokoshi, Y. Takahashi and H. Takeshima, *J. Antibiot*., **46**, 222 (1993); (c) K. Shiomi, H. Yang, J. Inokoshi, D.V. der Pyl, A. Nakagawa, H. Takeshima and S. Omura, *J. Antibiot*., **46**, 229 (1993).
2. (a) K. Hinterding, P. Hagenbuch, J. Retey and H. Waldmann, *Chem. Eur. J*., **5**, 227 (1999); (b) K. Hinterding, D. Alonso-Diaz and H. Waldmann, *Angew. Chem. Int. Ed*., **37**, 688 (1998); (c) M. Thutewohl and H. Waldmann, *Bioorg. Med. Chem*., **11**, 2591 (2003).
3. D.Q. Sun, P.X. Lai and W.D. Xie, *Synth. Commun*., **37**, 2989 (2007).
4. D.Q. Sun, *Turk. J. Chem*., **34**, 181 (2010).
5. (a) C. Liu, H.Q. Wang, B.M. Li and R.Y. Chen, *China J. Chin. Materia Med.*, **32**, 235 (2007); (b) N.J. Yu, S.X. Guo, S.Y. Xiao and F. Xie, *Chin. J. Chin. Materia Med*., **27**, 204 (2002).
6. A.K. Robin, D.C. Michael and A.M. Eugene, *Org. Lett*., **5**, 3683 (2003).
7. (a) A. Fryszkowska and R. Ostaszewski, *J. Heterocycl. Chem*., **45**, 765 (2008); (b) G. Gellerman, E. Hazan, T. Brider, T. Traube, A. Albeck and S. Shatzmiler, *Int. J. Pept. Res. Ther*., **14**, 183 (2008); (c) O. Neill, C. Jennifer and H.E. Blackwell, *Comb. Chem. High T. Scr*., **10**, 857 (2007); (d) M.B. Martins and I. Carvalho, *Tetrahedron*, **63**, 9923 (2007).